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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/921,004	ANDERSON ET AL.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-19,25,27,29-35 and 37-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-19, 25, 27, 29-35 and 37-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

The amendment filed April 16, 2004 is acknowledged and has been entered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1, 3-19, 25, 27, 29-35, and 37-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, part (b) the recitation "substantially all" is vague and indefinite. It is unclear what is considered to be substantially all. There is no definition provided for the term in the specification. See deficiencies throughout the claims. It is recommended to delete the recitation from the claims.

Claim 1, part (c) "greater than about 3kDa" is vague and indefinite. It is unclear what is considered to be greater than about. There is no description, definition or guidance provided for the term in the specification.

Claim 1, part (c) "below about" is vague and indefinite. It is unclear what is considered to be below about. There is no description, definition or guidance provided for the term in the specification.

Claim 27 is vague and indefinite because it is unclear what applicant is trying to do. Is applicant trying to establish a range which incorporates proteins that can be included

in a fraction or is applicant trying to establish a cut-off in which a fraction contains only the proteins, which fall within the range. Please clarify.

Claim 38 is vague and indefinite because it is unclear where in the process is the step of contacting a test biological fluid with said antibody against at least one of said proteins or peptides is occurring. Does it occur after step (a) or step (b) or step (c)?

Claim 39 is vague and indefinite because it is unclear if the two specific proteins are the same or different types of proteins. Please clarify.

Claim 41, "essentially all" is vague and indefinite. It is unclear what is considered to be essentially all. Is 99% considered essentially all, is 91% considered essentially all, is 82 % considered essentially all, Is any amount above 50% considered essentially all? Please clarify. Further, there is no definition provided for the term in the specification.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 3-5, 8, 9, 12-14, 17, 25 and 29, 30, 32-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stevens (US 6,410,692) in view of Liu et al (5,492,834).

Stevens discloses a method for removing interfering macromolecules from a liquid sample. Stevens et al disclose applying the sample to an affinity matrix to remove the interfering macromolecules. Stevens disclose centrifuging the sample. Stevens disclose recovering the liquid and subjecting the liquid sample to 2-D gel electrophoresis. Stevens disclose that the use of this 2-D gel electrophoresis allows for a large number of low abundant proteins to be identified and quantitated (col 12). Stevens discloses that a polypeptide affinity reagent is contacted with sample and binds to a macromolecule of interest. Stevens discloses that this polypeptide can be an antibody.

Stevens differ from the instant invention in failing to teach fractionating proteins in the fluid by molecular weight to produce a fractionated protein or peptide sample and separating a first fraction from the fractionated protein sample.

Liu et al disclose applying a liquid sample to a size exclusion gel. Liu et al disclose that the size exclusion gels have a molecular weight exclusion of at least 6,000. Liu et al disclose recovering a fraction of the fractioned sample and subjecting the sample to further analysis. The use of such an exclusion gel provides methods for analyzing body fluid samples for certain analytes while eliminating the effects of the presence of interfering components and provides for methods for analyzing patient urine samples for low concentrations of proteins indicative of certain disease states.

It would have been obvious to one of ordinary skill in the art to incorporate size exclusion gels as taught by Liu et al into the method of Stevens because Liu et al shows that the use of such an exclusion gel provides methods for analyzing body fluid samples for certain analytes while eliminating the effects of the presence of interfering components and provides for methods for analyzing patient samples for low concentrations of proteins indicative of certain disease states.

5. Claims 6 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stevens and Liu in view of Furst (US 5,926,387).

See above for teachings of Stevens and Liu et al.

Stevens and Liu et al differ from the instant invention in failing to teach zonal sedimentation centrifugation on density gradients.

Furst et al disclose a technique, which, involves layering a sample containing the components of interest onto the top of a liquid column, which is stabilized by a density-gradient of an inert solute. Furst et al disclose that this process is known as Rate-zonal sedimentation. Rate-zonal sedimentation is used to improve the efficiency of the fractionation by separating the particles according to size (col 1, lines 45-67).

It would have been obvious to one of ordinary skill in the art to incorporate rate-zonal sedimentation as taught by Furst et al into the modified method of Stevens because Furst et al shows that rate-zonal sedimentation improves the efficiency of the fraction by separating the particles according to size.

With respect to the stationary phases comprising different mesh sizes as recited in the instant claims, the mesh sizes can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. Further, it has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272,276, 205 USPQ 215, 218-219 (C.C.P.A. 1980).

6. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stevens and Liu et al in view of O'Donnnell et al (US 5,998,216).

See above for teachings of Stevens and Liu et al.

Stevens and Liu et al differ from the instant invention in failing to teach the addition of at least one protease inhibitor to the body fluid upon collection.

O'Donnell et al disclose the addition of protease inhibitor to urine. O'Donnell et al disclose that the addition of protease inhibitors to urine provides for maintaining and preserving the integrity of proteins and polypeptides present in a body fluid sample obtained ex-vivo (abstract). O'Donnell et al also disclose that these protease inhibitors provide a powerful effect on cytokines individually and collectively in human urine samples; and enhances markedly the stability and the preservation effect for the cytokines under a variety of different collection and environmental conditions (col 13, lines 1-56).

It would have been obvious to one of ordinary skill in the art to incorporate the use of a protease inhibitor such as taught by O'Donnell et al into the modified method of Stevens because O'Donnell et al shows the addition of protease inhibitors to urine provides for maintaining and preserving the integrity of proteins and polypeptides present in a body fluid sample obtained ex-vivo. O'Donnell et al also disclose that these protease inhibitors provide a powerful effect on cytokines individually and collectively in human urine samples; and enhances markedly the stability and the preservation effect for the cytokines under a variety of different collection and environmental conditions.

7. Claims 10, 11 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable

over Stevens and Liu et al in view of Opitech et al (Two-Dimensional SEC/RPLC Coupled to Mass Spectrometry for the Analysis of Peptides, Anal. Chem. 1997, 69, 2283-2291).

See above for teachings of Stevens and Liu et al.

Stevens and Liu et al differ from the instant invention in failing to specifically teach fractionating said first fraction by elution from a reverse phase stationary phase and identifying proteins or peptides by mass spectrometry.

Opiteck et al disclose methods for fractionating, separating, recovering and determining peptides. Opiteck et al disclose further fractionating a fraction by reversed phase liquid chromatography, which utilizes nonporous C-18 modified silica particles, which produce fast and efficient analyses. Opiteck also disclose identifying the peptide by mass spectrometry. Opiteck disclose that the use of RPLC and mass spectrometry provided for fast and efficient analyses of protein samples.

It would have been obvious to one of ordinary skill in the art to incorporate reversed phase liquid chromatography and mass spectrometry into the method of Stevens because Opiteck shows that the use of RPLC and mass spectrometry provided for fast and efficient analyses of protein samples.

8. Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stevens and Liu et al in view of Hage et al (Affinity Chromatography: A review of Clinical Applications, clinical Chemistry 45:5 593-615, 1999).

See above for teachings of Stevens and Liu et al.

Stevens and Liu et al differ from the instant invention in failing to teach further fraction from an affinity column.

Hage et al disclose methods comprising biological-like interactions for the separation and specific analysis of sample components. Hage et al disclose immunoaffinity columns and non-immunological affinity columns such as protein G and protein A. Hage et al disclose that affinity chromatography is rapidly becoming the separation method of choice in clinical laboratories and other biologically related fields such as pharmaceutical science and biotechnology. Hage et al disclose that affinity chromatography is an attractive alternative to traditional methods for the selective quantification and study of clinical samples and provides for the creation of an affinity system for almost any compound of clinical interest.

It would have been obvious to one of ordinary skill in the art to incorporate affinity chromatography as taught by Hage et al into the modified method of Stevens because Hage et al shows that affinity chromatography is an attractive alternative to traditional methods for the selective quantification and study of clinical samples and provides for the creation of an affinity system for almost any compound of clinical interest.

Response to Arguments

9. Applicant's arguments filed 04/16/2004 have been fully considered but they are not persuasive.

112 2nd Rejections

Applicant argues that the term "substantially all" is clear. Applicant argues that it is well known that whenever handling any mixture of protein that a small amount may be lost during handling and the performance of the fractionation based on molecular weight step. This is not found persuasive because as stated in the previous office action applicant does not provide a definition or description for the term in the specification.

Applicant argues that the term "greater than about 3kDa" is clear. Applicant directs Examiners attention to page 42, first paragraph gives guidance to remove salts and metabolic byproducts (not proteins or their degraded peptides and thus the functional goal for the limit is given. Applicant further states that the term is still definite on its face as a numerical value. This is not found persuasive because as stated on page 42, lines 15-22 of the specification, Two fractions were generated at > and < 30 kDa. Therefore, applicant has set the cut-off at 30. The applicant does not disclose greater than or equal to or less than or equal to 30. The applicant specifically states > 30 kDa and < 30 kDa. There is no guidance provided for greater than about or below about.

Applicant argues that claim 38 is definite because immunosubstraction step is performed after the molecular weight fractionation corresponding to between steps (c) and (d) and that it would be recognized that the step may be performed earlier between or with any steps after collection of the body fluid. This is not found persuasive because it is unclear how the molecular weight would not be affected by the addition of an antibody to the protein. For example, if the antibody is contacted with the protein before

the step of fractionating (step a). The protein or peptide would also comprise the additional weight of the antibody thus causing an elevation in molecular weight, which could effect how the protein or peptide is fractionated. Thus it appears that the addition would have to occur between steps (c) and (d).

103 Rejections

Applicant argues that Stevens and Liu et al are treating different types of samples. Applicant states that Stevens is treating serum whereas Liu et al is treating urine. Examiner agrees that Stevens is treating serum and Liu et al is treating urine, however, Stevens specifically states that the sample can be biological fluids which would encompass urine. Further, although Liu et al is treating urine, Liu et al specifically states that the sample can be serum (col 5, lines 43-48).

Applicant also argues that neither Stevens or Liu et al provides any suggestion to exclude proteins above an upper limit and that the present claims recite upper limits on the molecular weight of the proteins in the claimed fraction. This is not found persuasive because in the instantly recited claims the fraction does not exclude proteins of an upper limit. The instantly recited claims recite a first fraction from the fractionated protein or peptide sample, said first fraction having substantially all proteins or peptides recoverable from the body fluid with a molecular weight greater than about 3 kDa and below about 30,000 daltons. Therefore the claims only require that the fraction contain the proteins or peptides that fall within the range of 3 kDa to 30,000 daltons. There is no recitation establishing a cut-off above 30,000 daltons which would exclude proteins above 30,000 daltons. Therefore, the fraction can also contain proteins above the

recited range. Thus it is the Examiners position that the combination of Stevens and Liu et al reads on the instantly recited claims.

Applicant argues that neither Stevens nor Liu et al discloses removing plural specific predetermined proteins by using an affinity column containing plural specific bind agents as claimed in claim 29. From applicants stated arguments, it appears that Applicant may be trying to state that the column comprises different types of specific binding agents. This is not found persuasive because the instantly recited claims only require plural specific binding agents and Stevens discloses affinity columns which remove a predetermined interfering substance and one of ordinary skill would recognize that the affinity column would comprised more than a single affinity reagent (plural agents). The claim does not specify if the reagents are the same or different. Therefore, the combination of Stevens and Liu et al reads on the instantly recited claims.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary W. Counts
Examiner
Art Unit 1641
May 11, 2004

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